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RESEARCH ARTICLE

Status and timing of angiotensin receptor–neprilysin inhibitor implementation in patients with heart failure and reduced ejection fraction: Data from the Swedish Heart Failure Registry

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Aims We explored timing, settings and predictors of angiotensin receptor–neprilysin inhibitor (ARNI) initiation in a large, nationwide cohort of patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods and results Patients with HFrEF (ejection fraction <40%) registered in the Swedish HF Registry in 2017–2021 and naïve to ARNI were evaluated for timing and location of, and their characteristics at ARNI initiation. ARNI use increased from 8.3% in 2017 to 26.7% in 2021. Among 3892 hospitalized patients, 8% initiated ARNI in-hospital or ≤14 days after discharge, 4% between 15 and 90 days, and 88% >90 days after discharge or never initiated. Factors associated with earlier initiation included follow-up in specialized HF care, more severe HF, previous HF treatment use and higher income, whereas older age, higher comorbidity burden and living alone were associated with later/no initiation. Of 16 486 HFrEF patients, 8.1% inpatients and 5.9% outpatients initiated an ARNI at the index date. Factors associated with initiation in outpatients were overall consistent with those linked with an in-hospital/earlier ARNI initiation; 4.9% of 10 209 with HF duration <6 months and 9.1% of 5877 with HF duration ≥6 months initiated ARNI. Predictors of ARNI initiation in HF duration <6 months were inpatient status, lower ejection fraction, hypertension, whereas previous angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was associated with less likely initiation. Discontinuation at 1 year ranged between 13% and 20% across the above-reported analyses.

Conclusions In-hospital and early initiation of ARNI are limited in real-world care but still slightly more likely than in outpatients. ARNI were more likely initiated in patients with more severe HF, which might suggest its use as a second-line treatment and only following worsening of clinical status. One-year discontinuation rates were consistent regardless of the timing/setting of ARNI initiation.

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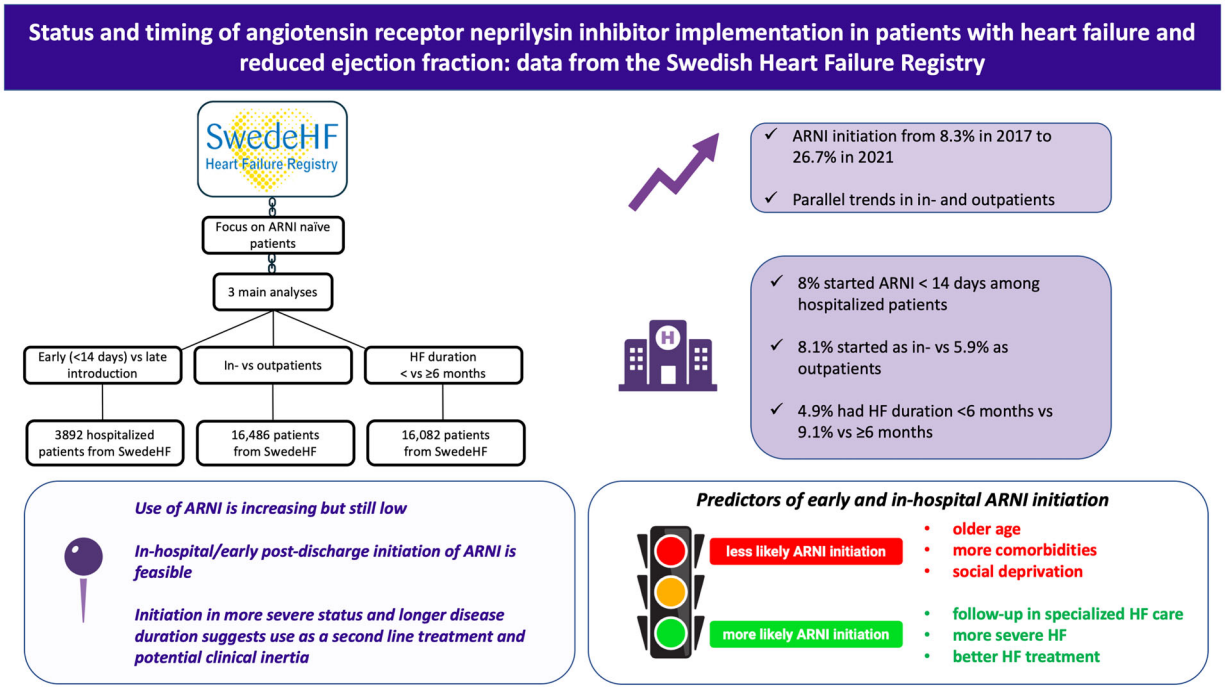
Graphical Abstract



Status and timing of angiotensin receptor–neprilysin inhibitor (ARNI) implementation in patients with heart failure (HF) with reduced ejection fraction in the Swedish Heart Failure Registry (SwedeHF).

Keywords Angiotensin receptor–neprilysin inhibitor • Guideline-directed medical therapy • Implementation • Heart failure • Heart failure with reduced ejection fraction • Sacubitril/valsartan

Introduction

Heart failure (HF) represents a global pandemic with growing prevalence and poor prognosis despite the availability of several life-saving pharmacological and device therapies.[1] The frequency of HF hospitalizations, together with the long in-hospital stay, impose a dramatic burden on healthcare systems worldwide, in terms of both human and financial resources.[1,2]

Guideline-directed medical therapy (GDMT) has traditionally been initiated slowly and sequentially; however, it is now recognized that early initiation of GDMT in HF with reduced ejection fraction (HFrEF) together with an early and well-structured clinical follow-up are associated in the outpatient setting with a reduction in mortality/morbidity.[3–6] Nevertheless, the implementation of GDMT in the real world remains often limited, and underprescription or delayed initiation is common.[1]

In the PARADIGM-HF trial, sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), significantly reduced cardiovascular (CV) mortality and HF hospitalizations compared with enalapril in stable patients with HFrEF, with a significant effect on the risk of HF hospitalizations after 30 days.[7,8] Therefore, sacubitril/valsartan received a class I recommendation for the treatment of chronic symptomatic HFrEF.[3,5,7] Additionally, in the PIONEER-HF, in-hospital initiation of ARNI in patients stabilized after an acute episode of HFrEF, with or without prior treatment with enalapril, led to a larger reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and, in exploratory analyses, also to a lower risk of HF readmissions compared with enalapril.[9] In the TRANSITION trial, initiation of sacubitril/valsartan in patients stabilized after an acute HF event, either in-hospital or shortly after discharge, was feasible and safe.[10] The overall limited evidence supporting the in-hospital initiation of ARNI has led to discrepant recommendations in the European and American guidelines, with only the latter recommending ARNI as *de novo* treatment in hospitalized patients with acute HF before discharge.[5] Nevertheless, the timing and modalities of ARNI introduction in the real world have been poorly explored.

Therefore, we aimed to investigate the timing and setting (in- vs. out of hospital) of, and patient profiles associated with, ARNI use in a large nationwide cohort of patients with HFrEF.

Methods

Data sources

The study population was selected from the Swedish HF Registry (SwedeHF). SwedeHF has been previously described.[11] Briefly, it is an ongoing voluntary healthcare quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are informed of registration and allowed to opt out. A majority of Swedish hospitals (69 out of 76 hospitals) and to a minor extent also primary care centres enrol patients as part of regular duty, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion is a diagnosis of HF according to the following International Classification of Diseases, Tenth Revision (ICD-10) codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. Coverage of SwedeHF in 2021 was 32% of the prevalent HF population in Sweden.[12] Linkage between SwedeHF and Statistics Sweden allowed to consider socioeconomic data, whereas the National Patient Register provided additional data on comorbidities (online supplementary *Table S1*). Use and timing of ARNI initiation was assessed through the National Prescribed Drug Register, which provides data on medications which are dispensed (and not only prescribed; online supplementary *Table S2*). Linkage between these registries was made possible by the personal identification number, which all residents in Sweden have. Index date for registration in SwedeHF was defined as the date of registration in SwedeHF, i.e. the date of the outpatient visit for outpatients and the date of discharge for inpatients.

Establishment of the HF registry and this analysis including the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

Study design

Three main analyses were designed and patients were grouped according to: analysis 1 – the timing of ARNI initiation following an HF hospitalization (in-hospital or ≤14 days after discharge vs. 15–90 days vs. >90 days or no use); analysis 2 – patient's location (in-hospital vs. outpatient) at ARNI initiation, and analysis 3 – duration of HF (<6 vs. ≥6 months) at ARNI initiation.

Patient characteristics associated with (1) an earlier vs. later/no ARNI initiation following an HF hospitalization, (2) an ARNI initiation as inpatients versus outpatients, and (3) ARNI initiation whether HF duration was <6 vs. ≥6 months, were also investigated.

We also assessed the temporal trends in ARNI initiation in the overall population and in inpatients versus outpatients, as well as the rates of ARNI discontinuation in all the performed analyses.

A sensitivity analysis excluding patients with contraindications to treatment with ARNI (i.e. estimated glomerular filtration rate <30 ml/min/1.73 m^2, systolic blood pressure <100 mmHg and serum potassium>5.5 mEq/L) was also performed. If patients had missing data for any variables related to the definition of contraindication, they were excluded from the sensitivity analysis as well.

Study population and definition of ARNI initiation and discontinuation

Patients with HFrEF (ejection fraction <40%) registered in SwedeHF between 1 January 2017 (approximate date of the approval of ARNI in Sweden) and 16 December 2021, with follow-up ≥14 days (to avoid immortal time bias due to the 14-day post-index definition used to capture ARNI from the National Prescribed Drug Register) were included. If a patient was registered more than once during the study period, the first registration was selected. Since the analyses focused on ARNI initiation, patients with prevalent use of ARNI were excluded, i.e. with an ARNI dispensation recorded in the National Prescribed Drug Register prior to the index date. Therefore, a patient was considered as initiating ARNI at the index date if a dispensation was recorded at the index date or within the following 14 days, allowing the time to collect the medication from the pharmacy following the outpatient visit/hospitalization.

Additional selection criteria were specifically considered for the following analyses: (1) only in-hospital patients with >30-day follow-up were included in the analysis on the timing of ARNI initiation following an HF hospitalization (analysis 1); (2) only patients with no missing information on HF duration (i.e. <6 vs. ≥6 months) were included in the analysis on ARNI initiation according to the duration of HF at the index date (analysis 3).

The flow-charts summarizing the cohort selection process are reported in online supplementary *Figure S1*. Discontinuation of treatment was assumed if no ARNI prescription was collected ≥5 months following a previously collected one. The time of discontinuation was then assumed to be the date of last prescription + 3 months.

Statistical analysis

Patient characteristics were reported as median (Q1–Q3) and compared by Kruskal–Wallis test if continuous, and as counts (percentages) and compared by chi-square test if categorical.

Temporal trends in ARNI use were calculated by considering as denominator the number of patients that at the middle of the year were registered in SwedeHF with the specified inclusion/exclusion criteria, regardless of ARNI use, and as numerator the number of patients that at the middle of the year were registered in SwedeHF with the specified inclusion/exclusion criteria and that had at least one ARNI dispensation during that year.

Multivariable logistic regression models were fitted to investigate patient characteristics independently associated with initiation/non-initiation of ARNI (variables included in the logistic regression models are marked with[a] in *Tables 1* and *3*). Results were reported as odds ratio (OR) with 95% confidence intervals (CI). Multiple imputation models (10 imputed datasets generated) were used to handle missing values for the variables included in the multivariable models (marked with[a] in *Tables 1* and *3*).

The discontinuation rate was estimated at 1 year by using the Kaplan–Meier method, and censoring at death or emigration from Sweden.

All statistical analyses were performed using R version 4.2.1 (R Core Team 2019). The code for the data management and statistical analyses performed is found at https://github.com/KIHeartFailure/swedehfarni. The level of significance was set to 5%, two-sided.

Results

ARNI use over time in the inpatient and outpatient setting

Overall there was a progressive increase over time in ARNI use (from 8.3% in HFrEF in 2017 to 26.7% in 2021), which was

Table 1 Characteristics of in-hospital patients stratified according to the timing of angiotensin receptor–neprilysin inhibitor initiation (analysis 1)

Variable	Missing (%)	0–14 days (*n* = 318, 8%)	15–90 days (*n* = 147, 4%)	>90 days/no treatment (*n* = 3427, 88%)	*p*-value
Demographic/organizational characteristics					
Male sex[a], *n* (%)	0.0	239 (75.2)	108 (73.5)	2316 (67.6)	0.009
Age, years, median (IQR)	0.0	65.0 (55.0–74.0)	68.0 (57.5–76.0)	75.0 (66.0–83.0)	<0.001
Age ≥75 years[a], *n* (%)	0.0	77 (24.2)	44 (29.9)	1763 (51.4)	<0.001
FU referral HF nurse clinic[a], *n* (%)	8.9	289 (94.1)	133 (97.8)	2323 (74.9)	<0.001
FU referral specialty care[a], *n* (%)	4.1	298 (95.2)	137 (94.5)	2502 (76.4)	<0.001
Time since HF hospitalization[a], *n* (%)	0.0				0.842
No		258 (81.1)	118 (80.3)	2703 (78.9)	
≤365 days		31 (9.7)	17 (11.6)	399 (11.6)	
>365 days		29 (9.1)	12 (8.2)	325 (9.5)	
HF duration ≥6 months[a], *n* (%)	3.4	82 (26.8)	35 (24.5)	1073 (32.4)	0.022
EF <30%[a], *n* (%)	0.0	231 (72.6)	106 (72.1)	1643 (47.9)	<0.001
NYHA class III–IV[a], *n* (%)	6.7	84 (63.6)	37 (56.1)	604 (46.7)	<0.001
MAP >90 mmHg[a], *n* (%)		124 (39.0)	74 (50.7)	1620 (47.5)	0.010
HR >70 bpm[a], *n* (%)	0.7	191 (60.4)	96 (65.3)	2141 (62.9)	0.558
Laboratory, *n* (%)					
eGFR <60 ml/min/1.73 m^2 [a]	0.7	76 (24.1)	30 (20.8)	1286 (37.8)	<0.001
NT-proBNP ≥ median[a]	17.3	167 (56.8)	80 (62.5)	1988 (71.1)	<0.001
Potassium[a]	0.9				0.353
Hyperkalaemia (>5 mEq/L)		5 (1.6)	4 (2.8)	67 (2.0)	
Normokalaemia (3.5–5.0 mEq/L)		299 (94.9)	132 (91.7)	3122 (91.9)	
Hypokalaemia (<3.5 mEq/L)		11 (3.5)	8 (5.6)	208 (6.1)	
Comorbidities					
BMI ≥30 kg/m^2 [a], *n* (%)	15.7	77 (28.1)	36 (27.7)	681 (23.7)	0.168
Smoking[a], *n* (%)	45.3	29 (16.3)	13 (14.1)	261 (14.0)	0.715
T2DM[a], *n* (%)	0.0	90 (28.3)	43 (29.3)	978 (28.5)	0.978
AF[a], *n* (%)	0.0	124 (39.0)	74 (50.3)	1867 (54.5)	<0.001
Ischaemic heart disease[a], *n* (%)	0.0	132 (41.5)	72 (49.0)	1741 (50.8)	0.006
Anaemia[a], *n* (%)	1.6	78 (24.8)	50 (34.7)	1329 (39.4)	<0.001
Hypertension[a], *n* (%)	0.0	179 (56.3)	97 (66.0)	2280 (66.5)	0.001
Peripheral artery disease[a], *n* (%)	0.0	30 (9.4)	14 (9.5)	310 (9.0)	0.957
Stroke[a], *n* (%)	0.0	33 (10.4)	18 (12.2)	467 (13.6)	0.245
Valve disease[a], *n* (%)	0.0	50 (15.7)	24 (16.3)	635 (18.5)	0.386
Cancer <3 years[a], *n* (%)	0.0	25 (7.9)	12 (8.2)	406 (11.8)	0.046
COPD[a], *n* (%)	0.0	21 (6.6)	11 (7.5)	419 (12.2)	0.003
Liver disease[a], *n* (%)	0.0	7 (2.2)	11 (7.5)	99 (2.9)	0.004
Charlson comorbidity index, median (IQR)	0.0	2.0 (1.0–4.0)	2.0 (1.0–4.0)	3.0 (1.0–4.0)	<0.001
Charlson comorbidity index, *n* (%)	0.0				0.00
0–1		121 (38.1)	48 (32.7)	978 (28/5)	
2–3		111 (34.9)	53 (36.1)	1212 (35.4)	
4–7		73 (23.0)	39 (26.5)	970 (28.3)	
≥8		139 (44.6)	61 (41.5)	1420 (42.4)	
Treatment, *n* (%)					
Previous ACEi/ARB[a]	0.0	162 (50.9)	88 (59.9)	1819 (53.1)	0.193
Beta-blockers[a]	0.2	300 (94.3)	139 (96.5)	3148 (92.0)	0.053
MRA[a]	0.4	203 (64.0)	99 (69.2)	1551 (45.4)	<0.001
SGLT2i[b]	90.9	31 (31.0)	4 (18.2)	34 (14.7)	0.003
Diuretics[a]	0.6	251 (79.2)	114 (79.2)	2711 (79.5)	0.985
Digoxin[a]	0.4	22 (6.9)	17 (11.8)	366 (10.7)	0.091
Antiplatelet therapy[a]	0.4	109 (34.3)	51 (35.4)	1233 (36.1)	0.798
Anticoagulant therapy[a]	0.5	152 (47.9)	72 (49.7)	1772 (51.9)	0.355
Statins[a]	0.3	149 (46.9)	87 (60.4)	1676 (49.0)	0.018
Nitrates[a]	0.4	17 (5.3)	8 (5.6)	309 (9.1)	0.033
ICD/CRT[a]	0.3	53 (16.7)	18 (12.4)	231 (6.8)	<0.001

Table 1 (Continued)

Variable	Missing (%)	0–14 days (*n* = 318, 8%)	15–90 days (*n* = 147, 4%)	>90 days/no treatment (*n* = 3427, 88%)	*p*-value
Socioeconomic characteristics, *n* (%)					
Family type living alone[a]	0.1	134 (42.1)	65 (44.2)	1745 (51.0)	0.004
Children[a]	0.0	254 (79.9)	121 (82.3)	2830 (82.6)	0.481
Education[a]	1.7				0.023
Compulsory school		98 (31.4)	53 (36.1)	1330 (39.5)	
Secondary school		139 (44.6)	61 (41.5)	1420 (42.2)	
University		75 (24.0)	33 (22.4)	618 (18.3)	
Income ≥ median[a]	0.1	196 (61.6)	81 (55.1)	1465 (42.8)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); FU, follow-up; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

[a]Included in imputation model and multivariable logistic and Cox regression models.

[b]Added to SwedeHF on 28 April 2021.

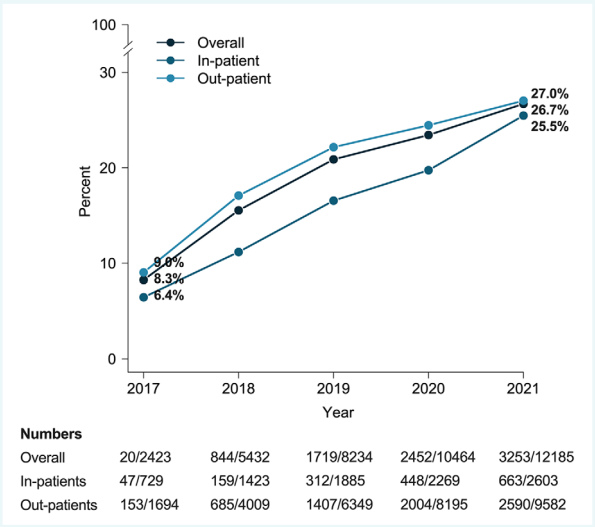


Figure 1 Temporal trends in angiotensin receptor–neprilysin inhibitor (ARNI) use in the overall cohort and in inpatients and outpatients. In the table, the denominator corresponds to the number of patients registered in SwedeHF and the numerator to the number of patients with at least one ARNI dispensation during that year (see statistical methods for further details).

observed both in inpatients (from 6.4% in 2017 to 25.5% in 2021) and outpatients (from 9.0% in 2017 to 27.0% in 2021) (*Figure 1*). Similar rates were observed when patients with contraindication/missing data for the variables related to the definition of contraindication to the treatment were excluded (online supplementary *Figure S2*).

Analysis 1: timing of ARNI initiation

Of 3892 hospitalized ARNI-naïve patients (median age 74 years [64–82], 31.6% female), 8% initiated ARNI during hospitalization or ≤14 days after discharge, 4% between 15 and 90 days, and 88% >90 days or never initiated (median follow-up 23.8 [0.0–59.0]). Data were consistent in the 3259 patients without contraindication/missing data for the variables related to the definition of contraindication to treatment with ARNI (7% during hospitalization or ≤14 days after discharge, 4% between 15 and 90 days, and 89% >90 days or never initiated).

Patient characteristics of the overall cohort and stratified according to the timing of ARNI initiation are summarized in *Table 1*.

Key patient characteristics independently associated with more likely ARNI initiation ≤14 days versus >90 days or no initiation were a more recent registration in SwedeHF, follow-up in specialty care and HF nurse-led clinic and a higher income, a lower ejection fraction, higher New York Heart Association (NYHA) class, history of peripheral artery disease, previous use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), use of mineralocorticoid receptor antagonists (MRA), oral anticoagulants, and having an implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT). Older age, higher mean arterial pressure, history of atrial fibrillation/flutter, anaemia, chronic obstructive pulmonary disease and living alone versus cohabitating were instead associated with lower likelihood of ARNI initiation ≤14 days. Later registration in SwedeHF, younger age, follow-up in HF nurse-led clinic, lower ejection fraction, previous use of ACEi/ARB, use of MRA and statins and liver disease were associated with higher likelihood of initiating ARNI between 15 and 90 versus 90 days after a hospitalization (*Figure 2*).

Rates of ARNI discontinuation at 1 year in patients initiating treatment during hospitalization or ≤14 days after discharge and in those initiating between 15 and 90 days were 17.2% (95% confidence interval [CI] 14.5–19.7) and 14.9% (95% CI 12.1–17.6), respectively.

Analysis 2: location of ARNI initiation

Of 16 486 HFrEF patients registered in SwedeHF during the study period (24% inpatients and 76% outpatients), 8.1% of inpatients

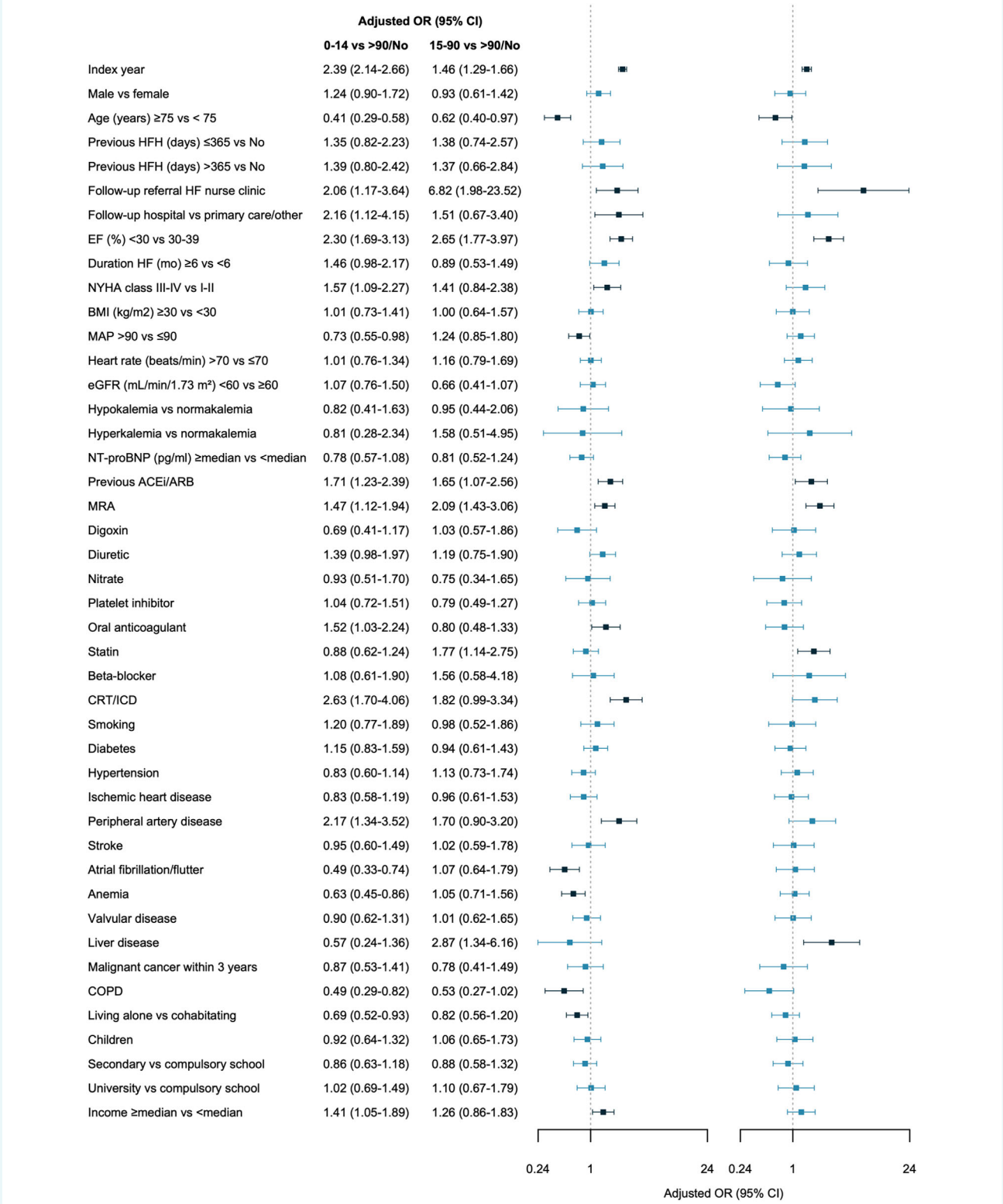


Figure 2 Patient characteristics associated with earlier versus later/no angiotensin receptor–neprilysin inhibitor initiation. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.

and 5.9% of outpatients initiated ARNI within 14 days of the index date. Consistent results were observed in the 13 949 patients without contraindications/missing data for the variables related to the definition of contraindication to ARNI (7.6% of inpatients and 6.2% of outpatients).

Patient characteristics stratified according to the timing of ARNI initiation within the inpatient and outpatient subpopulations are summarized in *Table* 2.

Key patient characteristics independently associated with ARNI initiation regardless of patient's location were male sex, follow-up in specialty care, more severe NYHA class and higher income, whereas anaemia was associated with lower likelihood. Concomitant MRA use and a previous ICD/CRT implantation were more likely associated with ARNI initiation in outpatients versus inpatients; older age was more strongly associated with lower likelihood but a more recent registration in SwedeHF with a higher likelihood of ARNI initiation in inpatients versus outpatients. Lower ejection fraction was associated with more likely ARNI initiation, whereas ischaemic heart disease, atrial fibrillation and chronic obstructive pulmonary disease with less likely ARNI initiation, in inpatients but not in outpatients. Finally, longer HF duration and worse renal function were associated with more likely ARNI initiation in outpatients but not in inpatients (*Figure* 3).

Discontinuation rates at 1 year in patients initiating ARNI as inpatients versus outpatients were 18.2% (95% CI 12.6–23.5) and 17.0% (95% CI 13.9–19.9), respectively.

Analysis 3: initiation according to duration of heart failure

Of the 16 086 patients with HFrEF without missing data on HF duration, including both in- and outpatients, 63% had an HF duration <6 months (median age 73 years [64–80], 29.3% female). Of them, 4.9% initiated ARNI versus 9.1% of those with HF duration ≥6 months. In the sensitivity analysis including 13 618 patients without contraindication/missing data for the variables related to the definition of contraindication to ARNI, among patients with HF duration <6 months (65%) 4.8% initiated ARNI versus 9.9% of those with HF duration ≥6 months.

Patient characteristics according to HF duration and ARNI initiation are reported in *Table* 3.

Younger age and referral to specialty care predicted ARNI initiation more likely whether HF duration was ≥6 months rather than <6 months; later year of registration in SwedeHF was more likely in patients with HF duration <6 months rather than ≥6 months. Inpatient status, lower ejection fraction, hypertension and nitrate use were independently associated with initiation in HF duration <6 months but not ≥6 months. Referral to HF nurse-led clinic and higher income predicted initiation only if HF duration was ≥6 months. Previous ACEi/ARB use was associated with more likely ARNI initiation in HF duration ≥6 months and less likely initiation in HF duration <6 months (*Figure* 4).

Rates of ARNI discontinuation at 1 year were 13.4% (95% CI 9.6–17.0) in HF duration <6 months versus 19.9% (95% CI 16.2–23.4) in HF duration ≥6 months.

Discussion

Over the last few years the management of HFrEF has transitioned from a sequential approach to a strategy of upfront initiation of the four pillars of GDMT followed by up-titration to maximal tolerated doses according to the patient profile.[3–5] Randomized controlled trials on the most novel pharmacological classes (i.e. ARNI and sodium–glucose cotransporter 2 inhibitors [SGLT2i]) have highlighted an early prognostic benefit associated with the use of these treatments, and by revisiting older trials, similar early benefits were found also for ACEi/ARB, beta-blockers and MRAs.[13,15,16] The STRONG-HF trial demonstrated that an intensive strategy of GDMT initiation was feasible and resulted in a better implementation of HF treatments and outcome in patients admitted for acute decompensated HF.[14] Nevertheless, in routine care multiple barriers hamper the rapid initiation/intensification of HF treatments, and especially their introduction in patients at discharge.[17]

In this study, we provided an overview on the magnitude and settings of ARNI initiation in a nationwide real-world cohort with HFrEF, demonstrating that: (i) the overall use of ARNI in HFrEF in clinical practice is increasing but remains relatively low (i.e. <30% as of 2021); (ii) initiation of ARNI during hospitalization or early after hospital discharge is not common, as only 8% of ARNI-naïve inpatients started ARNI in-hospital or within 14 days after hospital discharge, but is still slightly more common than an initiation as outpatient (i.e. ∼6%); (iii) ARNI treatment is more likely initiated later during the course of the disease; (iv) patient profiles associated with an earlier/in-hospital initiation of ARNI were overall consistent with those observed in the outpatient setting, and were characterized by younger age, more severe HF, HF-dedicated follow-up and receiving overall more optimized HF treatment; and (v) discontinuation rates at 1 year ranged between ∼15% and 20% regardless of the timing/setting of ARNI initiation (*Graphical Abstract*).

Timing and location of ARNI initiation

European and American guidelines differ concerning the recommended timing of ARNI initiation in HFrEF due the different interpretation of available evidence. In particular, American guidelines suggest to initiate ARNI as *de novo* treatment in hospitalized patients with acute decompensated HFrEF before discharge, whereas European guidelines do acknowledge the possibility of adopting this approach, but more strongly highlight the low level of the supporting evidence (IIb B).[3,5] The efficacy/safety of ARNI in hospitalized patients has been investigated in only two studies adopting surrogate endpoints and enrolling a total of ∼1500 patients.[9,10] However, both studies demonstrated the safety of this approach, and in the PIONEER-HF trial in-hospital initiation of ARNI led to a more rapid and intense reduction in NT-proBNP levels and potentially lower rates of CV death/HF hospitalization.[9,18,19] Implementation of ARNI in daily clinical practice has been reported to be lower compared with SGLT2i,[20,21] although the rate of patients with chronic HFrEF eligible to receiving this drug according to trial and labelling criteria is higher than expected.[22,23] In the Get With The Guidelines-HF, among patients hospitalized with HF

Table 2 Characteristics of patients initiating vs. not initiating angiotensin receptor–neprilysin inhibitor according to the patient's location (inpatient vs. outpatient) (analysis 2)

Variable	Missing (%)	Inpatient			Outpatient		
		No ARNI (*n* = 3645, 92%)	ARNI (*n* = 323, 8%)	*p*-value	No ARNI (*n* = 11 776, 94%)	ARNI (*n* = 742, 6%)	*p*-value
Demographic/organizational characteristics							
Male sex[a], *n* (%)	0.0	2475 (67.9)	243 (75.2)	0.008	8335 (70.8)	587 (79.1)	<0.001
Age, years, median (IQR)	0.0	75.0 (66.0–83.0)	66.0 (55.0–74.0)	<0.001	73.0 (64.0–80.0)	71.0 (63.0–77.0)	<0.001
Age ≥75 years[a], *n* (%)	0.0	1862 (51.1)	80 (24.8)	<0.001	5133 (43.6)	285 (38.4)	0.006
Inpatient[a], *n* (%)	0.0	–	–	–	–	–	–
FU referral HF nurse clinic[a], *n* (%)	4.3	2486 (75.4)	294 (94.2)	<0.001	10 754 (93.9)	705 (96.4)	0.007
FU referral specialty care[a], *n* (%)	2.3	2668 (76.6)	303 (95.3)	<0.001	10 045 (86.8)	708 (96.9)	<0.001
Time since HF hospitalization[a], *n* (%)	0.0			0.458			<0.001
No		2862 (78.5)	262 (81.1)		6627 (56.3)	353 (47.6)	
≤365 days		431 (11.8)	31 (9.6)		4085 (34.7)	209 (28.2)	
>365 days		352 (9.7)	30 (9.3)	0.458	1064 (9.0)	180 (24.3)	
HF duration ≥6 months[a], *n* (%)	2.4	1784 (48.9)	236 (73.1)	<0.001	1147 (32.6)	82 (26.4)	0.029
EF <30%[a], *n* (%)	0.0	2668 (76.6)	303 (95.3)	<0.001	1784 (48.9)	236 (73.1)	<0.001
NYHA class III–IV[a], *n* (%)	22.4	658 (47.6)	86 (63.7)	<0.001	3908 (36.9)	341 (49.6)	<0.001
MAP >90 mmHg[a], *n* (%)	2.0	1721 (47.4)	128 (39.6)	0.009	5915 (51.5)	365 (50.6)	0.650
HR >70 bpm[a], *n* (%)	2.4	2280 (63.0)	195 (60.7)	0.467	5833 (51.0)	322 (45.4)	0.004
Laboratory, *n* (%)							
eGFR <60 ml/min/1.73 m^2[a]	2.5	1364 (37.7)	79 (24.6)	<0.001	3516 (30.9)	248 (33.8)	0.099
NT-proBNP ≥ median[a]	18.8	2115 (71.0)	170 (56.9)	<0.001	4152 (43.9)	263 (41.0)	0.164
Potassium[a]	2.5			0.098			0.410
Hyperkalaemia (>5 mEq/L)		3311 (91.7)	304 (95.0)		10 690 (94.3)	678 (93.1)	
Normokalaemia (3.5–5.0 mEq/L)		227 (6.3)	11 (3.4)		225 (2.0)	16 (2.2)	
Hypokalaemia (<3.5 mEq/L)		74 (2.0)	5 (1.6)		425 (3.7)	34 (4.7)	
Comorbidities							
BMI ≥30 kg/m^2[a], *n* (%)	18.0	730 (23.8)	78 (28.1)	0.132	2429 (25.3)	187 (32.4)	<0.001
Smoking[a], *n* (%)	24.1	277 (14.0)	29 (16.1)	0.496	1126 (11.5)	58 (9.7)	0.205
T2DM[a], *n* (%)	0.0	1042 (28.6)	93 (28.8)	0.989	2855 (24.2)	247 (33.3)	<0.001
AF[a], *n* (%)	0.0	1988 (54.5)	126 (39.0)	<0.001	5876 (49.9)	394 (53.1)	0.098
Ischaemic heart disease[a], *n* (%)	0.0	1860 (51.0)	135 (41.8)	0.002	5538 (47.0)	424 (57.1)	<0.001
Anaemia~[a], *n* (%)	10.1	1419 (39.6)	78 (24.5)	<0.001	2827 (27.5)	150 (23.0)	0.014
Hypertension[a], *n* (%)	0.0	2428 (66.6)	182 (56.3)	<0.001	7502 (63.7)	529 (71.3)	<0.001
Peripheral artery disease[a], *n* (%)	0.0	333 (9.1)	30 (9.3)	1.000	944 (8.0)	60 (8.1)	1.000
Stroke[a], *n* (%)	0.0	507 (13.9)	33 (10.2)	0.077	1319 (11.2)	99 (13.3)	0.084
Valve disease[a], *n* (%)	0.0	677 (18.6)	52 (16.1)	0.305	1743 (14.8)	107 (14.4)	0.818
Cancer <3 years[a], *n* (%)	0.0	432 (11.9)	25 (7.7)	0.033	1439 (12.2)	90 (12.1)	0.988
COPD[a], *n* (%)	0.0	437 (12.0)	22 (6.8)	0.007	1200 (10.2)	76 (10.2)	1.000
Liver disease[a], *n* (%)	0.0	110 (3.0)	7 (2.2)	0.487	259 (2.2)	8 (1.1)	0.055
Charlson comorbidity index, median (IQR)	0.0	3.0 (1.0–4.0)	2.0 (1.0–4.0)	<0.001	2.0 (1.0–4.0)	2.0 (1.0–4.0)	0.052
Charlson comorbidity index, *n* (%)	0.0			<0.001			<0.001
0–1		1038 (28.5)	123 (38.1)		3959 (33.6)	204 (27.5)	
2–3		1285 (35.3)	113 (35.0)		4386 (37.2)	316 (42.6)	
4–7		1034 (28.4)	73 (22.6)		2752 (23.4)	193 (26.0)	
≥8		288 (7.9)	14 (4.3)		679 (5.8)	29 (3.9)	
Treatment, *n* (%)							
Previous ACEi/ARB[a]	0.0	1954 (53.6)	164 (50.8)	0.357	10 881 (92.4)	689 (92.9)	0.700
Beta-blockers[a]	0.1	3347 (92.1)	304 (94.1)	0.228	10 966 (93.2)	713 (96.1)	0.003
MRA[a]	0.1	1676 (46.2)	206 (64.0)	<0.001	5442 (46.2)	529 (71.4)	<0.001
SGLT2i[b]	89.0	44 (16.1)	35 (33.3)	<0.001	262 (19.9)	55 (43.7)	<0.001
Diuretics[a]	0.2	2883 (79.6)	255 (79.2)	0.928	7787 (66.2)	499 (67.3)	0.548
Digoxin[a]	0.2	2883 (79.6)	255 (79.2)	0.928	991 (8.4)	71 (9.6)	0.309
Antiplatelet therapy[a]	0.2	1304 (36.0)	112 (34.7)	0.690	3968 (33.7)	256 (34.5)	0.027
Anticoagulant therapy[a]	0.2	1883 (51.9)	155 (48.1)	0.212	5860 (49.8)	409 (55.1)	0.076
Statins[a]	0.1	1802 (49.6)	153 (47.4)	0.477	6140 (52.2)	476 (64.2)	0.045
Nitrates[a]	0.2	327 (9.0)	17 (5.3)	0.029	733 (6.2)	60 (8.1)	0.053
ICD/CRT[a]	0.5	1065 (9.1)	207 (27.9)	<0.001	1065 (9.1)	207 (27.9)	<0.001

Table 2 (Continued)

Variable	Missing (%)	Inpatient			Outpatient		
		No ARNI ($n = 3645$, 92%)	ARNI ($n = 323$, 8%)	*p*-value	No ARNI ($n = 11\,776$, 94%)	ARNI ($n = 742$, 6%)	*p*-value
Socioeconomic characteristics							
Family type living alone[a]	0.2	5275 (44.9)	297 (40.1)	0.012	1841 (50.6)	136 (42.1)	0.004
Children[a]	0.0	9746 (82.8)	624 (84.1)	0.376	3012 (82.6)	259 (80.2)	0.302
Education[a]	1.4			0.001			0.005
Compulsory school		3943 (33.9)	208 (28.5)		1418 (39.6)	100 (31.5)	
Secondary school		5218 (44.9)	331 (45.4)		1509 (42.1)	140 (44.2)	
University		2462 (21.2)	190 (26.1)		658 (18.4)	77 (24.3)	
Income ≥ median[a]	0.2	6015 (51.2)	453 (61.1)	<0.001	1567 (43.0)	199 (61.6)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); EF, ejection fraction; FU, follow-up; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

[a]Included in imputation model and multivariable logistic and Cox regression models.

[b]Added to SwedeHF on 28 April 2021.

20.8% fulfilled all the selection criteria of the PIONEER-HF trial, and the characteristics of the eligible patients only modestly differed when compared with those enrolled in the trial, which could support that an earlier initiation of ARNI might be more often considered.[24]

In our study, ARNI were initiated in only ~8% of patients at or <14 days after hospital discharge, with most patients initiating treatment after 90 days or never, and in-hospital initiation was even slightly more frequent than in the outpatient setting (i.e. ~6%). Patients initiated with ARNI within or earlier after an HF hospitalization discharge, as well those initiating as outpatients, had the same characteristics as those who are usually observed and receiving better implemented GDMT, i.e. younger age, follow-up in HF-dedicated care, less comorbidities and better socioeconomic status,[20,21] which is quite expected. However, they were also more likely to have more severe HF, which might indicate: (i) that at least part of the limited implemented use of ARNI is explained by clinical inertia, which might be overcome whether the patient is sicker; (ii) that use of ARNI is considered as second-line treatment, i.e. whether the clinical status of the patient worsens; (iii) that in more advanced care, where also knowledge about available evidence might be more spread, the approach of an earlier initiation is perceived as safe even in more challenging clinical conditions. Patient profiles associated with in-hospital/earlier initiation were overall consistent with those initiating ARNI in the outpatient setting, highlighting that the barriers to the timely implementation of treatment might be the same as those to the overall initiation of ARNI regardless of patient's location.

Our results are also consistent with those from the multinational cohort of the EVOLUTION-HF study where the implementation of novel GDMT, including ARNI and SGLT2i, following a hospitalization for HF was delayed compared with renin–angiotensin–aldosterone system inhibitors and beta-blockers, suggesting that inertia or more cautiousness toward newer treatment might play a role.[17] However, in a follow-up analysis of the same study, the limited implementation of ARNI did not change over time whereas SGLT2i use improved.[25] In our cohort although the implementation of ARNI was overall limited, it showed signals of improvement over time, i.e. increased three-fold from 2017 to 2021 with similar magnitude in inpatients and outpatients.

ARNI initiation according to duration of heart failure

Rapid implementation of GDMT is a key recommendation of all recent international HF guidelines.[3,5] The evidence supporting the effect of ARNI in promoting left ventricular reverse remodelling derives from studies including patients with a relatively recent diagnosis of HF, suggesting that the effects of ARNI might be even more beneficial in the earlier stages of the disease.[26] According to the 2021 ESC guidelines on HF, ARNI treatment is recommended as a replacement for an ACEi/ARB, and there is only a low class of recommendation (IIb) and level of evidence (B) for initiation in patients *de novo* or naïve to ACEi/ARB.[3] This approach, which inevitably leads to a later initiation of ARNI or might even lead to no initiation due to clinical inertia, is mainly linked with the limited evidence on *de novo* use of ARNI given the run-in phase with enalapril in the PARADIGM-HF.[7] However, in the PIONEER-HF, where no run-in periods were performed, the improvement in NT-proBNP levels with ARNI was consistent in patients with and without previous history of HF and in those with and without prior use of ACEi or ARB, but only limited data are available on harder endpoints, which might be due to the low power to detect differences in clinical events in subgroups.[9,27] In the TRANSITION study enrolling patients initiating ARNI following an acute decompensated HFrEF event even if not prior ACEi or ARB users, initiation of ARNI in newly diagnosed HF patients, alongside the initiation of other GDMT was feasible and associated

Table 3 Characteristics of patients initiating versus not initiating angiotensin receptor–neprilysin inhibitor according to the duration of heart failure (analysis 3)

Variable	Missing (%)	HF duration <6 months			HF duration ≥6 months		
		No ARNI (*n* = 9709, 95%)	ARNI (*n* = 500, 5%)	*p*-value	No ARNI (*n* = 5339, 91%)	ARNI (*n* = 538, 9%)	*p*-value
Demographic/organizational characteristics							
Male sex[a], *n* (%)	0.0	6669 (68.7)	370 (74.0)	0.014	3888 (72.8)	439 (81.6)	<0.001
Age, years, median (IQR)	0.0	72.0 (62.0–79.0)	67.0 (56.8–76.0)	<0.001	76.0 (69.0–82.0)	71.0 (64.0–78.0)	<0.001
Age ≥75 years[a], *n* (%)	0.0	3833 (39.5)	148 (29.6)	<0.001	2965 (55.5)	208 (38.7)	<0.001
Inpatient[a], *n* (%)	0.0	2374 (24.5)	229 (45.8)	<0.001	1147 (21.5)	82 (15.2)	0.001
FU referral HF nurse clinic[a], *n* (%)	4.2	8703 (92.5)	472 (95.9)	0.006	4246 (85.0)	502 (95.8)	<0.001
FU referral specialty care[a], *n* (%)	2.3	8571 (89.8)	476 (95.8)	<0.001	3850 (74.8)	510 (97.1)	<0.001
Time since HF hospitalization[a], *n* (%)	0.0			<0.001			<0.001
No		6662 (68.6)	385 (77.0)		2552 (47.8)	211 (39.2)	
≤365 days		2904 (29.9)	103 (20.6)		1543 (28.9)	132 (24.5)	
>365 days		143 (1.5)	12 (2.4)		1244 (23.3)	195 (36.2)	
HF duration ≥6 months[a], *n* (%)							
EF <30%[a], *n* (%)	0.0	4287 (44.2)	313 (62.6)	<0.001	2071 (38.8)	237 (44.1)	0.020
NYHA class III–IV[a], *n* (%)	22.0	2722 (34.7)	176 (49.4)	<0.001	1753 (45.0)	246 (54.1)	<0.001
MAP >90 mmHg[a], *n* (%)	2.0	5082 (53.0)	249 (50.7)	0.354	2354 (45.7)	232 (43.9)	0.476
HR >70 bpm[a], *n* (%)	2.4	5370 (56.1)	280 (56.8)	0.790	2541 (49.7)	221 (43.2)	0.007
Laboratory, *n* (%)							
eGFR <60 ml/min/1.73 m^2[a]	2.5	2498 (26.2)	121 (24.4)	0.402	2261 (44.2)	199 (37.5)	0.003
NT-proBNP ≥ median[a]	18.8	4059 (50.9)	231 (50.2)	0.814	2042 (48.9)	191 (41.8)	0.005
Potassium[a]	3.0			0.856			0.216
Hyperkalaemia (>5 mEq/L)		8949 (94.1)	463 (93.5)		4704 (92.7)	494 (93.9)	
Normokalaemia (3.5–5.0 mEq/L)		304 (3.2)	18 (3.6)		143 (2.8)	8 (1.5)	
Hypokalaemia (<3.5 mEq/L)		261 (2.7)	14 (2.8)		225 (4.4)	24 (4.6)	
Comorbidities							
BMI ≥30 kg/m^2[a], *n* (%)	17.5	2037 (24.6)	125 (29.0)	0.044	1068 (25.8)	135 (33.1)	0.002
Smoking[a], *n* (%)	23.6	973 (12.4)	48 (13.0)	0.784	397 (10.9)	36 (9.3)	0.368
T2DM[a], *n* (%)	0.0	2125 (21.9)	142 (28.4)	0.001	1674 (31.4)	189 (35.1)	0.081
AF[a], *n* (%)	0.0	4533 (46.7)	206 (41.2)	0.019	3115 (58.3)	299 (55.6)	0.232
Ischaemic heart disease[a], *n* (%)	0.0	3874 (39.9)	210 (42.0)	0.375	3334 (62.4)	337 (62.6)	0.967
Anaemia[~a], *n* (%)	10.1	2453 (27.8)	106 (22.1)	0.008	1683 (36.0)	115 (24.6)	<0.001
Hypertension[a], *n* (%)	0.0	5733 (59.0)	316 (63.2)	0.073	3925 (73.5)	377 (70.1)	0.096
Peripheral artery disease[a], *n* (%)	0.0	642 (6.6)	30 (6.0)	0.656	604 (11.3)	56 (10.4)	0.575
Stroke[a], *n* (%)	0.0	925 (9.5)	48 (9.6)	1.000	844 (15.8)	79 (14.7)	0.535
Valve disease[a], *n* (%)	0.0	1211 (12.5)	52 (10.4)	0.192	1140 (21.4)	99 (18.4)	0.123
Cancer <3 years[a], *n* (%)	0.0	1102 (11.4)	50 (10.0)	0.391	724 (13.6)	61 (11.3)	0.168
COPD[a], *n* (%)	0.0	868 (8.9)	40 (8.0)	0.522	727 (13.6)	58 (10.8)	0.076
Liver disease, *n* (%)[a]	0.0	224 (2.3)	7 (1.4)	0.240	138 (2.6)	8 (1.5)	0.157
Charlson comorbidity index, median (IQR)	0.0	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.361	3.0 (2.0–5.0)	3.0 (2.0–4.0)	0.001
Charlson comorbidity index, *n* (%)	0.0			0.561			<0.001
0–1		3785 (39.0)	205 (41.0)		1115 (20.9)	114 (21.2)	
2–3		3527 (36.3)	181 (36.2)		1988 (37.2)	239 (44.4)	
4–7		1931 (19.9)	96 (19.2)		1766 (33.1)	161 (29.9)	
≥8		466 (4.8)	18 (3.6)		470 (8.8)	24 (4.5)	

Table 3 (Continued)

Variable	Missing (%)	HF duration <6 months			HF duration ≥6 months		
		No ARNI (*n* = 9709, 95%)	ARNI (*n* = 500, 5%)	*p*-value	No ARNI (*n* = 5339, 91%)	ARNI (*n* = 538, 9%)	*p*-value
Treatment, *n* (%)							
Previous ACEi/ARB[a]	0.0	7827 (80.6)	336 (67.2)	<0.001	4706 (88.1)	499 (92.8)	0.002
Beta-blockers[a]	0.1	9066 (93.5)	474 (94.8)	0.272	4915 (92.2)	517 (96.1)	0.001
MRA[a]	0.1	4273 (44.1)	313 (62.6)	<0.001	2685 (50.4)	404 (75.4)	<0.001
SGLT2i[b]	88.9	220 (19.2)	67 (39.4)	<0.001	85 (20.2)	21 (38.9)	0.003
Diuretics[a]	0.2	6485 (66.9)	354 (71.1)	0.060	3938 (73.9)	382 (71.0)	0.155
Digoxin[a]	0.1	805 (8.3)	33 (6.6)	0.204	536 (10.1)	57 (10.6)	0.749
Antiplatelet therapy[a]	0.2	3383 (34.9)	178 (35.6)	0.787	1765 (33.1)	184 (34.3)	0.634
Anticoagulant therapy[a]	0.2	4556 (47.0)	238 (47.6)	0.835	2984 (56.0)	310 (57.6)	0.503
Statins[a]	0.1	4666 (48.1)	255 (51.0)	0.226	3089 (58.0)	362 (67.3)	<0.001
Nitrates[a]	0.2	438 (4.5)	29 (5.8)	0.220	594 (11.2)	47 (8.7)	0.101
ICD/CRT[a]	0.5	321 (3.3)	39 (7.8)	<0.001	974 (18.4)	214 (39.8)	<0.001
Socioeconomic characteristics, *n* (%)							
Family type living alone[a]	0.2	4380 (45.2)	200 (40.0)	0.025	2546 (47.8)	222 (41.3)	0.005
Children[a]	0.0	7997 (82.4)	410 (82.0)	0.881	4465 (83.6)	449 (83.5)	0.966
Education[a]	1.4			0.018			<0.001
Compulsory school		3157 (32.9)	140 (28.5)		2067 (39.3)	160 (30.2)	
Secondary school		4419 (46.1)	224 (45.6)		2164 (41.2)	240 (45.4)	
University		2012 (21.0)	127 (25.9)		1024 (19.5)	129 (24.4)	
Income ≥ median[a]	0.2	5170 (53.4)	320 (64.0)	<0.001	2248 (42.2)	316 (58.8)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); EF, ejection fraction; FU, follow-up; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

[a]Included in imputation model and multivariable logistic and Cox regression models.

[b]Added to SwedeHF on 28 April 2021.

with a better risk–benefit profile than in patients with prior HFrEF.[10]

In our cohort, less ARNI initiation was observed in patients with shorter versus longer history of HF (<6 vs. ≥6 months, i.e. <5% vs. 9.1%). When we explored the differences in predictors of treatment initiation, patients with shorter HF history had higher likelihood of being treated with ARNI if hospitalized as probably considered more safe or signal of decompensation, and whether had more severe HF as probably considered more needed, and whether had hypertension as probably considered a marker of better tolerability. Notably, previous ACEi/ARB use was associated with more likely initiation of ARNI in patients with an HF duration ≥6 months, which might highlight that ARNI are often considered as a second-line treatment and initiated only later if the clinical status of the patient worsens.

Discontinuation of treatment with ARNI

Low implementation of GDMT in daily clinical practice can be explained by missed prescription but also by treatment discontinuation which can be explained by tolerability issues or patient's poor adherence. In the PARADIGM-HF, 10.7% of patients receiving ARNI discontinued the treatment due to tolerability issues, with corresponding estimates being 19.7% in the in-hospital setting of the PIONEER-HF prematurely.[7,9] In the TITRATION study, which was designed to test the tolerability of an earlier ARNI initiation, the discontinuation rate was 11.9% over 12-week follow-up. Patients encountered in daily clinical practice show several characteristics, including older age, more comorbidities and use of polypharmacy, which can further increase the likelihood of tolerability issues and drug discontinuation. In our real-world study, discontinuation rates approximated 15–20% at 1 year, regardless of the timing/setting of initiation. Interestingly, in SwedeHF 1-year discontinuation rates for SGLT2i were comparable (i.e. 20%), despite the better expected tolerability as compared with ARNI.[20] Overall consistent results were also shown in the larger and multicenter EVOLUTION-HF study (i.e. 26% for ARNI and 23% for SGLT2i).[17] These findings might be explained by (i) the reasons for treatment discontinuation being more often related with misconceptions on the long-term indications for treatment, overall fear for potential side effects and overall poor patient's adherence rather than the real drug's safety profile[28]; and/or (ii) patients switching

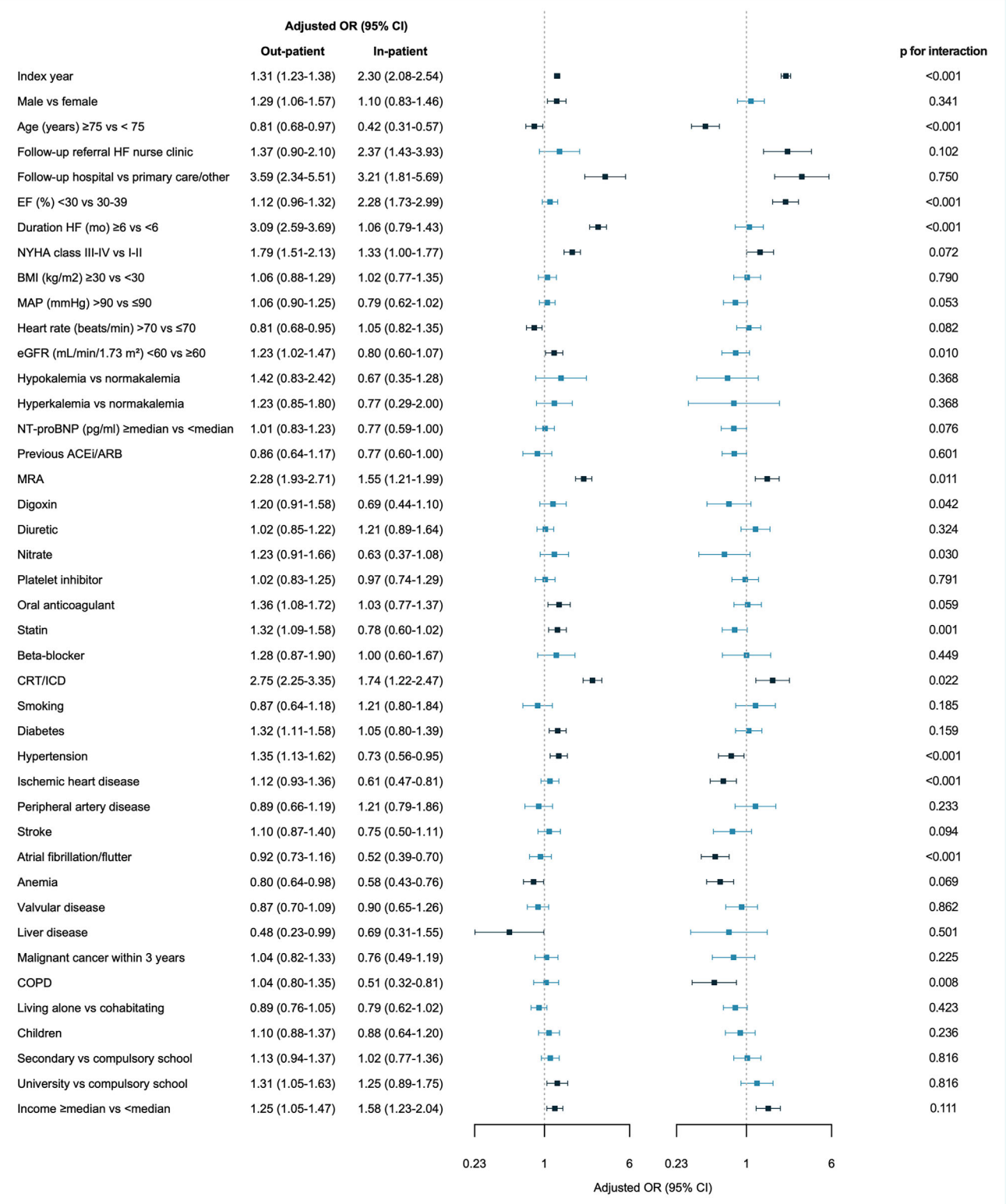


Figure 3 Predictors of angiotensin receptor–neprilysin inhibitor initiation according to the patient's location (in- vs. outpatient). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.

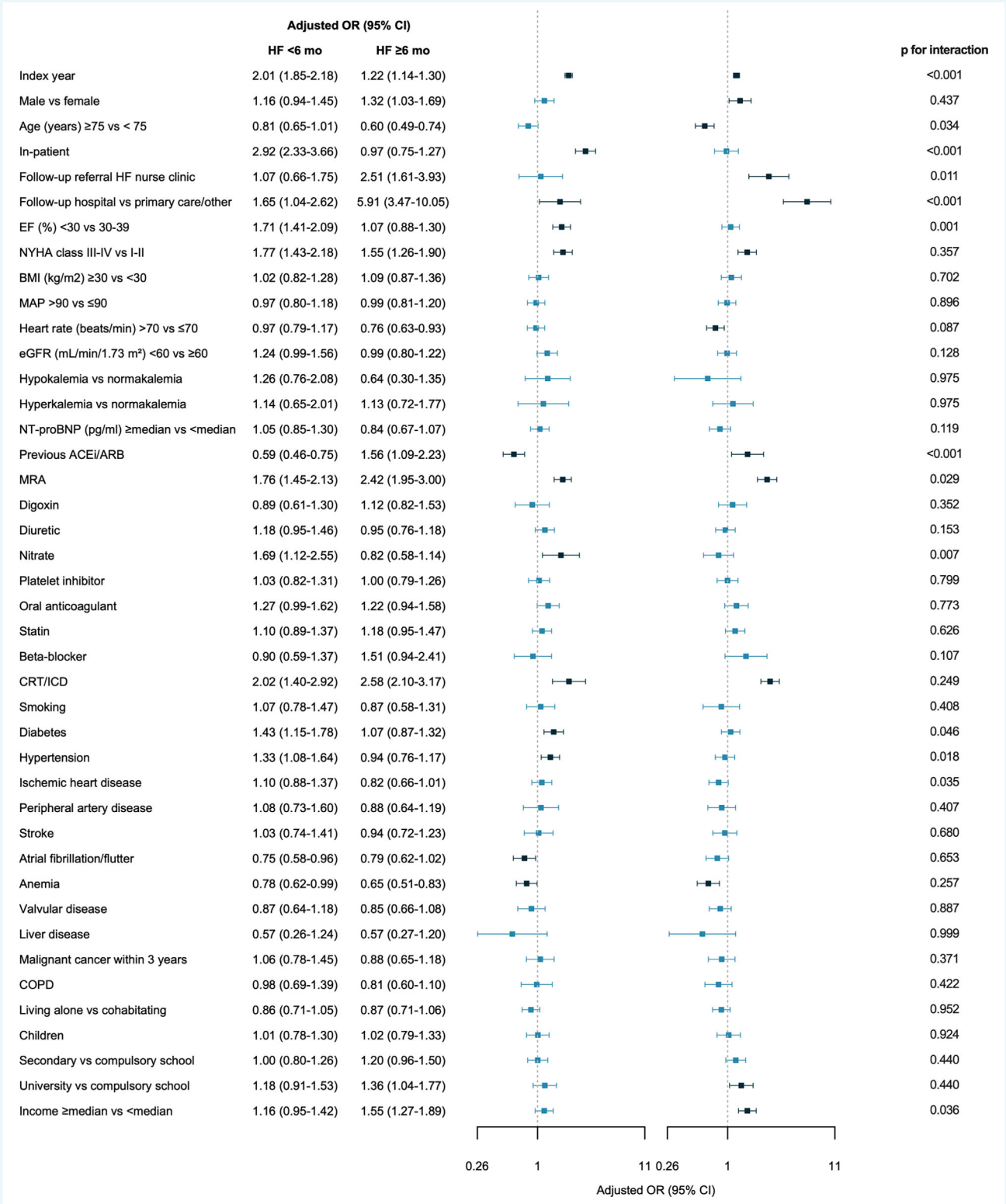


Figure 4 Predictors of angiotensin receptor–neprilysin inhibitor initiation according to the duration of heart failure (HF). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.

from ACEi/ARB to ARNI and therefore selected for being more tolerant at least in terms of blood pressure spending function.[29,30]

Limitations

This was an observational study and therefore a role for residual confounding when assessing associations cannot be ruled out. No data on tolerability and adverse effects were available. Coverage of the SwedeHF is around 30% and our study is based on a nationwide cohort, which might affect the generalizability of our results to the general HF population and different settings of care.

Conclusions

In this nationwide HFrEF cohort, use of ARNI increased over time but remained overall low. The initiation of ARNI during, or early after, hospitalization was overall limited but still slightly more likely than in outpatients, highlighting the feasibility and safety of this approach. *De novo* or recently diagnosed patients were less likely initiated with ARNI, with the majority of patients initiating treatment only later during their disease course. Patient characteristics linked with better care and more severe HF were linked with overall and earlier initiation, which might highlight clinical inertia and initiation of treatment only if the clinical status of the patient worsens. Discontinuation rates were overall consistent regardless of the initiation timing/setting.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;**118**:3272–3287. https://doi.org/10.1093/cvr/cvac013
2. Stolfo D, Lund LH, Benson L, Hage C, Sinagra G, Dahlstrom U, *et al.* Persistent high burden of heart failure across the ejection fraction spectrum in a nationwide setting. *J Am Heart Assoc* 2022;**11**:e026708. https://doi.org/10.1161/JAHA.122.026708
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
4. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, *et al.* Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:872–881. https://doi.org/10.1002/ejhf.2206
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
6. Khan MS, Fonarow GC, Greene SJ. Guideline-directed medical therapy for heart failure: The key ingredient for successful in-hospital and post-discharge care. *Eur J Heart Fail* 2024;**26**:355–358. https://doi.org/10.1002/ejhf.3152
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.*; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004. https://doi.org/10.1056/NEJMoa1409077
8. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.*; PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015;**131**:54–61. https://doi.org/10.1161/CIRCULATIONAHA.114.013748
9. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, *et al.*; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–548. https://doi.org/10.1056/NEJMoa1812851
10. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, *et al.*; TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: Primary results of the randomised TRANSITION study. *Eur J Heart Fail* 2019;**21**:998–1007. https://doi.org/10.1002/ejhf.1498
11. Savarese G, Vasko P, Jonsson A, Edner M, Dahlstrom U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci* 2019;**124**:65–69. https://doi.org/10.1080/03009734.2018.1490831
12. SwedeHF Annual Report; 2022. https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh/arsrapporter-sh-aldre/arsrapport-2022 Accessed 3 July 2024.
13. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail* 2021;**23**:882–894. https://doi.org/10.1002/ejhf.2149
14. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
15. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, *et al.* Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol* 2021;**6**:499–507. https://doi.org/10.1001/jamacardio.2020.7585
16. Desai AS, Claggett BL, Packer M, Zile MR, Rouleau JL, Swedberg K, *et al.*; PARADIGM-HF Investigators. Influence of sacubitril/valsartan (LCZ696) on 30-day readmission after heart failure hospitalization. *J Am Coll Cardiol* 2016;**68**:241–248. https://doi.org/10.1016/j.jacc.2016.04.047
17. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegard J, Lund LH, *et al.* Heart failure drug treatment – inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;**11**:1–14. https://doi.org/10.1016/j.jchf.2022.08.009
18. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, *et al.* Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial.

Circulation 2019;**139**:2285–2288. https://doi.org/10.1161/CIRCULATIONAHA.118.039331
19. DeVore AD, Braunwald E, Morrow DA, Duffy CI, Ambrosy AP, Chakraborty H, *et al.*; PIONEER-HF Investigators. Initiation of angiotensin-neprilysin inhibition after acute decompensated heart failure: Secondary analysis of the open-label extension of the PIONEER-HF trial. *JAMA Cardiol* 2020;**5**:202–207. https://doi.org/10.1001/jamacardio.2019.4665
20. Stolfo D, Lund LH, Benson L, Lindberg F, Ferrannini G, Dahlstrom U, *et al.* Real-world use of sodium-glucose cotransporter 2 inhibitors in patients with heart failure and reduced ejection fraction: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:1648–1658. https://doi.org/10.1002/ejhf.2971
21. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, *et al.* Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail* 2022;**24**:1047–1062. https://doi.org/10.1002/ejhf.2483
22. Savarese G, Hage C, Benson L, Schrage B, Thorvaldsen T, Lundberg A, *et al.* Eligibility for sacubitril/valsartan in heart failure across the ejection fraction spectrum: Real-world data from the Swedish Heart Failure Registry. *J Intern Med* 2021;**289**:369–384. https://doi.org/10.1111/joim.13165
23. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, *et al.*; Heart Failure Long-Term Registry Investigators. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: Bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. *Eur J Heart Fail* 2019;**21**:1383–1397. https://doi.org/10.1002/ejhf.1532
24. Fudim M, Sayeed S, Xu H, Matsouaka RA, Heidenreich PA, Velazquez EJ, *et al.* Representativeness of the PIONEER-HF clinical trial population in patients hospitalized with heart failure and reduced ejection fraction. *Circ Heart Fail* 2020;**13**:e006645. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006645
25. Bozkurt B, Savarese G, Adamsson Eryd S, Bodegard J, Cleland JGF, Khordoc C, *et al.* Mortality, outcomes, costs, and use of medicines following a first heart failure hospitalization: EVOLUTION HF. *JACC Heart Fail* 2023;**11**:1320–1332. https://doi.org/10.1016/j.jchf.2023.04.017
26. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.*; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019;**322**:1085–1095. https://doi.org/10.1001/jama.2019.12821
27. Ambrosy AP, Braunwald E, Morrow DA, DeVore AD, McCague K, Meng X, *et al.*; PIONEER-HF Investigators. Angiotensin receptor-neprilysin inhibition based on history of heart failure and use of renin-angiotensin system antagonists. *J Am Coll Cardiol* 2020;**76**:1034–1048. https://doi.org/10.1016/j.jacc.2020.06.073
28. Greene SJ, Khan MS, Butler J. Why do clinicians not prescribe quadruple medical therapy for heart failure with reduced ejection fraction? *Eur J Heart Fail* 2024;**26**:338–341. https://doi.org/10.1002/ejhf.3133
29. Bohm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, *et al.* Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF. *Eur Heart J* 2017;**38**:1132–1143. https://doi.org/10.1093/eurheartj/ehw570
30. Vardeny O, Claggett B, Kachadourian J, Pearson SM, Desai AS, Packer M, *et al.* Incidence, predictors, and outcomes associated with hypotensive episodes among heart failure patients receiving sacubitril/valsartan or enalapril: The PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). *Circ Heart Fail* 2018;**11**:e004745. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004745